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Prognostic significance of infectious episodes occurring during first-line therapy for diffuse large B-cell lymphoma – A nationwide cohort study

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Abstract

Infections during first-line therapy for DLBCL are often associated with chemotherapy dose reductions and increased mortality. Systemic infections have also been suggested as beneficial promotors of immunological responses. However, whether there is an association between the timing of an infectious episode and outcome during treatment has not yet been clarified. We investigated how the occurrence and timing of infectious episodes during the 1st line of treatment for 'de novo' DLBCL influenced patient outcome.

We used data on DLBCL patients from the Danish Lymphoma Registry, the Danish National Patient Registry and the Danish National Pathology Registry. Infections were categorized according to type (ICD-10) and time of occurrence after treatment start. 'Early' infections were defined as occurring between days 7-42 and 'late' infections between days 100-150 from treatment start. Patients experiencing both 'early and late' infections, were categorized separately. We used multivariable Cox regression and Kaplan-Meier estimates to assess the association between infections and survival adjusting for NCCN-IPI, sex, comorbidity, and rituximab treatment. We identified 3,546 patients, median age 65 years (IQR 56;73). Infectious episodes occurred in 1,171 (33%) patients, of which 666 had 'early', 303 'late', and 202 both 'early and late' events. Patients without registered infections had a 5-year overall survival (OS) rates of 74%. Those with 'early', 'late', or 'early+late' had 5-year OS of 65%, 62%, and 53%, respectively. Compared with patients without any registered infections, hazard rate ratios (HR) were 1.24 (95% CI 1.05-1.47), 1.32 (95% CI 1.06-1.63) and 1.59 (95% CI 1.27-2.00), respectively in the multivariable model.

We observed that infectious episodes during first line-treatment for 'de novo' DLBCL occurred in 44% of the patients. Irrespective of timing, patients with infectious episodes had an inferior outcome compared to those without. Outcome patterns was similar for patients registered with sepsis.

Introduction

Treatment with cytotoxic chemo-immunotherapy has, besides an intended tumoricidal effect, also an unintended toxic side effect on the tissues and cells of both the innate and the adaptive immune system.(1,2) Well recognized common toxicities include mucosal barrier injury and neutropenia, which jointly set the stage for infectious complications.(3–5) Febrile neutropenia and sepsis are among the most common clinical syndromes associated with hospitalization in cancer patients undergoing chemotherapy and are known to negatively impact outcome.(6) This is especially true in elderly and/or otherwise frail patients e.g. those with comorbid conditions.(7,8) On the other hand, spontaneous regressions of malignant lesions observed after acute febrile/septic episodes have been described and are suggested to reflect an activation of anti-tumoral effects from the host's immune system such as chimeric antigen receptor (CAR) T-cell therapy and check point protein modulation.(9–15) In terms of timing, most existing studies show that the majority of infectious complications, recorded under induction chemotherapy for DLBCL, occur early in the course of treatment and most frequently after the first cycle.(8,16,17)

To elucidate, whether the occurrence of an infectious episode and its timing ('early', 'late' or 'early and late') during first-line therapy for DLBCL has an impact on outcome, we investigated a nationwide, population-based cohort of 3,546 *'de* novo*'* DLBCL patients identified through the Danish Lymphoma Registry.

Methods

Setting

Denmark has a population of approximately 5.7 million inhabitants and all residents have access to free tax-supported health care. More specifically, cancer therapy, including

supportive care and medicine (e.g. antibiotics, growth factors and immunoglobulins), is free of cost.

Registries

Danish registries are unique in term of quality, coverage and completeness and they reflect the health care utilization of the population on a nationwide level.(18) We used four nationwide Danish medical databases to conduct this population-based cohort study: (i) the Civil Registration system (CRS), (ii) the Danish National Patient Registry (DNPR), (iii) the Danish Lymphoma Registry (LYFO), and (iv) the Danish National Pathology Registry. The CRS uses a unique 10-digit Civil Persons Register (CPR) number, assigned to every citizen upon birth or immigration and this number is a key component of register-based research in Denmark, since it serves as the common identifier that allows cross-linkage across all Danish medical and administrative registers and clinical databases.(19,20) Data on vital status were obtained from the CRS, where this data is updated on a daily basis for all Danish citizens.(21) Information on the occurrence of diagnoses of infection was obtained from the DNPR, which is a comprehensive nationwide hospital register recording, for each citizen, every contact with the hospital system along with parameters such as primary diagnosis, treatments given, and paraclinical examinations performed (e.g. blood tests and diagnostic imaging).(22,23) Lymphoma-specific information was retrieved from the LYFO-registry, which prospectively registers patients with lymphoid malignancies, referred to the lymphoma-treating hematology departments in Denmark. LYFO includes 95% of all lymphoma patients in Denmark and has a completeness of registered variables of 99%, and positive predictive values for variables ranging from 88% to 99%.(24) Variables contained in the LYFO registry include lymphoma histology (according to The International Classification of Disease for Oncology third edition

histology codes [ICD-O-3]), date of diagnosis, Ann Arbor stage, paraclinical findings, International Prognostic Index (IPI), antineoplastic treatment, response to therapy etc.(25) Pathology reports for all patients were retrieved from the Danish National Pathology Registry, which contains detailed descriptions of all pathology specimens analyzed in Denmark since 1997. This register is also used to identify those very few lymphoma patients that are not captured by the LYFO registry.(26)

Patients and covariates

From LYFO we included patients diagnosed with 'de novo' DLBCL, between January 1, 2000 and December 31, 2012, that had been treated with anthracycline containing chemotherapy with or without rituximab. Patients were excluded if they had a diagnosis of primary central nervous system (CNS)-lymphoma, if lymphoma was diagnosed at autopsy or if information on antineoplastic therapy was missing. From the LYFO registry, we extracted baseline patient characteristics including information on sex, age, Ann Arbor stage, extra nodal disease, plasma lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status, and treatment regimens. Furthermore, we identified date of diagnosis, first treatment, and where applicable, clinical relapse and start of relapse treatment. Pathology reports of the primary as well as the relapse biopsies from all patients were obtained from the Danish National Pathology Registry and were used to cross-validate the date of diagnosis. The Pathology Registry was also used to confirm whether a bone marrow biopsy actually was performed and, if so, whether it showed lymphoma infiltration. For relapse biopsies, we obtained information on the biopsy date and relapse histology. To assess the level of comorbidity, a Charlson Comorbidity Index (CCI) was computed based on DNPR diagnoses recorded up to ten years before the onset of DLBCL.(27) We used the nineteen diagnoses from

the original CCI publication and defined three levels of comorbidity: CCI score 0 (No comorbidity), 1-2 (moderate) or >2 (severe). DNPR data for assessment of comorbidity has been validated for the time period covering this study.(28) The National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) was calculated as described in the original publication.(29) This prognostic index includes the same covariates as the original IPI (age, ECOG performance status, serum lactate dehydrogenase level, extra nodal sites and Ann Arbor stage).(30) In addition, the NCCN-IPI refines age in four age strata (≤40, 41-60, 61-75, >75 years), LDH in three strata (LDH-ratio≤1, LDH-ratio>1-3 and LDH-ratio>3), and it uses information on extra nodal disease from four specified sites, i.e. bone marrow, CNS, liver/gastrointestinal tract and lung.

Exposure

From the DNPR we obtained information date and duration of admissions with a primary diagnosis of infection according to the International Classification of Diseases 10th revision (ICD-10)(see Table S2 for codes).(22,23) We restricted our search to admissions for infection with a duration of at least 24 hours to secure that the infection had a certain level of seriousness. Infections were categorized according to day of admission in the treatment period. Infection was defined as 'early' if the admission with infection was registered between days 7-42 and 'late', if it occurred between days 100-150. The definition of 'early' infections as those occurring between days 7 and 42 from treatment start, reflects the period from the first potential nadir (day 7, e.g. in a bi-weekly R-CHOP schedule) to the start of the 3rd course (day 42, e.g. in a tri-weekly R-CHOP schedule). Similarly, the definition of 'late' infectious episodes reflects the period after the start of the 6th course until the end of the nadir after the 8th course (day 150, e.g. in a tri-weekly R-CHOP x 8 schedule). Patients with infectious episodes which occurred both early and late were categorized as a separate group. Based on the

diagnosis codes, we classified the infectious diagnoses into eleven categories reflecting organ involvement, major clinical syndromes and clinical severity. The eleven categories were: Febrile neutropenia, sepsis, pneumonia, infections of the CNS, upper airway infections, gastrointestinal and urinary tract infections, infections of the skin- and other soft tissues, mouth infections, unspecified fever, and other infectious conditions (Table S2). The eleven categories were also used to register the more serious infection if a patient had more than one diagnose of infection registered on discharge, i.e. sepsis was used instead of skin infection if both were registered. In a sensitivity analysis, considering a severe and prevalent infection, we examined the outcomes for patients registered with sepsis.

Statistics

Baseline demographics are presented as counts and percentages for all patients and according to the time period of infection (early, late, early and late, or none). Data on continuous variables are presented as median and inter quartile range (IQR). Each category of infection and the total count among patients are presented according to time periods. We used the Kaplan-Meier method and Cox proportional hazards regression analysis to assess the association of occurrence and timing of episodes of infection with overall survival (OS) and event free survival (EFS), patients without infection were used as reference.(31,32) In order to avoid immortal time bias patients were followed from 150 days after diagnosis to death from any cause (OS), while EFS was measured as time to relapse, retreatment registered by the clinician with or without biopsy, or death. We adjusted for NCCN-IPI (4 groups), sex, rituximab treatment (yes/no), and level of comorbidity (3 groups). We also conducted analyses stratified by sex, age (<61 vs≥61 years) and rituximab treatment (yes/no). All estimates were calculated with 95% confidence intervals (95%CI). The proportional hazards assumption was evaluated graphically with log minus log plots and was accepted. We used the STROBE statement to guide the

reporting of our study.(33)

Statistical analyses were performed using Stata/IC 14.2 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). This study was approved by the Danish Data Protection Agency (1-16-02-562-13) and the Danish Health and Medicines Authority (3-3013-1079/1/).

Results

We identified 3,546 patients (Figure 1) who fulfilled the inclusion criteria. Patients had a median age of 65 years (quartiles 56;73) and 56% were men. Detailed patient characteristics are shown in Table 1 for all patients and Table S4 for patients in the survival analysis. In total, 1,551 (44%) patients had at least one infection registered within 150 days from beginning their treatment; 666 (19%) patients had an early infection, 303 (9%) a late, 202 (6%) both an early and a late infection . In the time period between early and late 380 (11%) patients had an episode of infection registered. Patients with 'only early' or 'only late' infection had a similar distribution of NCCN-IPI score, sex, and comorbidity index, while patients with 'both early and late' infection more often had advanced disease with extranodal involvement, poor performance status, elevated LDH, and a higher CCI score. Patients receiving rituximab treatment constituted 75% of the total cohort reflecting the time period of the study. Within the 'early' infection group, the fraction of rituximab treated patients was slightly higher (82%) than the one of the 'late' and 'early + late' infection groups (76% and 79%, respectively). Figure S1 illustrates the time periods investigated. Table 2 displays the categories of the first infection, both in total and according to the timing in the course of treatment (early, late or early + late. The 1,171 patients had a total of 1,641 infections, 821 (70.1%) patients had one, 253 (21.6%) two, 77 (6.6%) three, and the remaining 20 patients had four or more diagnoses of infection recorded in the DNRP (Table S3). Febrile neutropenia (34%), septicemia (17%), and pneumonia (14%) were the most common categories of infection both in the case of early and of later

infections. Among the patients with septicemia, 77% were registered with unspecified sepsis, and 7% with sepsis due to gram-negative infection (Table S2).

Survival

Within the first 150 days, 373 patients died. At a median follow-up time of 7.9 years, 942 (30%) died and 1,134 (34%) had a relapse registered, with or without biopsy, or died. As shown in Table 3 and figure 2, patients without registered infectious episodes had a 5-year OS probability of 74% (95% CI 72-75). In comparison, those with 'early', late and early+late infections had a 5-year OS probability of 65% (95% CI 61-69), 62% (95% CI 56-68), and 53% (95% CI 45-60), respectively, with corresponding adjusted hazard rate ratios of 1.24 (95% CI 1.05-1.47), 1.32 (95% CI 1.06-1.63) and 1.59 (95% CI 1.27-2.00). The results of the stratified analysis revealed that infection was associated with an increased mortality, particularly for women, as shown in Figure 3 and Table S1. However, patients younger than 60 years with early infection tended to have a superior outcome, HR 0.93 (95% CI 0.64-1.36) compared to patients without infection, but the CI is broad due to small numbers. Furthermore, patients treated with CHOP did not have inferior outcome if infection was registered. In a sensitivity analysis looking at patients registered with an episode of sepsis, we observed a similar pattern of outcome as in patients with registered infection overall. The group without sepsis had the best outcome, early and late had intermediate outcomes, and patients with sepsis in both time periods had the worst outcome (Figure S2).

Discussion

In this nationwide study of 'de novo' DLBCL patients, we found that patients with infection, no matter the time period, had an inferior outcome compared to those without. Therefore, our data do not support the hypothesis of a possible beneficial anti-tumoral role of an infection early or late during the treatment of DLBCL. We found that one third of the patients had a

diagnose of infection registered in a cumulated period of 85 days during treatment and 44% during the first 150 days. The observation that early infection in patients 60 years or younger has a HR of 0.93 was based on few observations with a correspondingly wide confidence interval and does not, as a single observation, confirm our hypothesis, and could represent a chance finding. The negative impact on outcome was pronounced in patients above 60-years. Older age has in several studies proved to be a risk factor for infection and the EORTC recognizes age above 60 years as a an important risk factor for febrile neutropenia.(34) Also in rituximab treated patients both early and late infection had a negative prognostic impact and we observed that rituximab treated patients with both early and late infections had a particularly low 5 year OS. A possible explanation could be that rituximab eliminates the healthy CD20-positive lymphocyte population resulting in decreased concentration of immunoglobulins with a consequent increased risk of infection.(35,36) A further contribution to this observation may be the increasing dose intensity given to elderly patients with DLBCL in more recent years. We recently showed that anthracycline containing therapy was administered in 71% of patients above 74 years, in the period from 2008 to 2012, compared to only 57% between 2003 and 2007.(37) The more frequent use of anthracyclines in patients above 74 years seen in recent years probably reflects a combination of factors, such as a more fit elderly population, better supportive strategies and a consequent shift towards a more curatively intended approach in the elderly.

The strengths of this study include the population-based design with an almost complete prospective inclusion of all DLBCL patients treated with curative intent in Denmark over a recent 12-year period with well-covered long-term follow-up. Patients have unfettered access to cancer treatment and follow-up programs in the public health care system including access to hospitals in case of infectious complications and no private practice of cancer treatment

exists in Denmark. This virtually eliminates a selection towards more healthy patients into our cohort. The LYFO registry has recently been validated and showed high completeness and positive predictive values for selected variables above 95%.(24) One of the limitations of our study was the lack of validation of the registered infection diagnoses. However, the incidence of infections in our study is in accordance with observations from both randomized clinical trials (RCT) and observational data, where occurrence of grade 3 or 4 infections range from around 20% in RCTs and 50% in observational studies.(2,38–41) Moreover, a recent validation study showed that the positive predictive value of an infection diagnosis in cancer patients registered in the DNPR ranged from 84% for 'sepsis' to 93% for 'pneumonia'.(42) We included only admissions with infection lasting more than 24 hours as infectious admissions to secure that the included infections had a certain degree of seriousness. It is possible that some admissions lasting more than 24 hours, which accordingly were categorized as "no infection" also were serious infections which would bias our estimates towards no difference. The proportion of patients registered with infection in our study, however, argues against a high degree of misclassification. Another limitation lies in the somewhat arbitrary definition of 'early' and 'late' occurrence, considering the heterogeneity of treatment timelines reflected by e.g. patients who received chemoimmunotherapy on a bi- or tri-weekly basis or patients who had their treatment schedule delayed by excessive toxicities.

Conclusion

This is, to our knowledge, the largest study examining the prognostic impact of register-based infections in DLBCL patients within the rituximab era. We conclude that infectious episodes did not seem to have an antineoplastic effect translating into a survival advantage for DLBCL patients. DLBCL patients in general, and elderly DLBCL patients in particular, face a high risk of therapy-related infections, and the adverse impact on outcome from these complications

seem to add prognostic information to well-established prognosticators such as NCCN-IPI and the Charlson Comorbidity Index. These findings provide an insight and a rationale for tailoring adjuvant supportive approaches such as antimicrobial prophylaxis, use of growth factors and immunoglobulin substitution, particularly in elderly patients.

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Conflict of interest statement

The authors have no conflicts of interest directly relevant for the present study

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Tables

Table 1.Baseline patient characteristics

	None		Early		Late		Early and late		Total	
	N	%	N	%	N	%	N	%	N	%
All	2,375	(100)	666	(100)	303	(100)	202	(100)	3,546	(100)
Sex										
Women	1,019	(43)	309	(46)	144	(48)	96	(48)	1,568	(44)
Men	1,356	(57)	357	(54)	159	(52)	106	(52)	1,978	(56)
Age										
Median age in years (IQR)	64	(55;72)	68	(59;76)	65	(55;73)	65	(58;74)	65	(56;73)
≤40 years	172	(7)	42	(6)	30	(10)	13	(6)	257	(7)
41-60 years	766	(32)	160	(24)	78	(26)	50	(25)	1,054	(30
61-75 years	1,034	(44)	294	(44)	136	(45)	101	(50)	1,565	(44)
>75 years	403	(17)	170	(26)	59	(19)	38	(19)	670	(19)
Ann Arbor stage										
I-II	1,123	(47)	264	(40)	108	(36)	58	(29)	1,553	(44)
III-IV	1,252	(53)	402	(60)	195	(64)	144	(71)	1,993	(56)
Lactate dehydrogenase (× ULN)										
LDH-R ≤1	1,183	(50)	261	(39)	126	(42)	67	(33)	1,637	(46)
LDH-R >1-3	951	(40)	329	(49)	139	(46)	116	(57)	1,535	(43)
LDH-R >3	170	(7)	62	(9)	27	(9)	16	(8)	275	(8)
Missing	71	(3)	14	(2)	11	(4)	3	(1)	99	(3)
Performance (ECOG)										
0-1	1,979	(83)	493	(74)	227	(75)	151	(75)	2,850	(80)
≥2	378	(16)	170	(26)	75	(25)	50	(25)	673	(19)
Missing	18	(1)	3	(<1)	1	(<1)	1	(<1)	23	(1)
Extra nodal disease										
Not present	1,616	(68)	399	(60)	185	(61)	108	(53)	2,308	(65)
Present	759	(32)	267	(40)	118	(39)	94	(47)	1,238	(35)
NCCN-IPI										
Low risk	335	(14)	46	(7)	21	(7)	5	(2)	407	(11)
Low – Intermediate risk	973	(41)	226	(34)	111	(37)	68	(34)	1,378	(39)
High-Intermediate risk	768	(32)	278	(42)	126	(42)	97	(48)	1,269	(36)
High risk	221	(9)	101	(15)	34	(11)	29	(14)	385	(11)
Missing	78	(3)	15	(2)	11	(4)	3	(1)	107	(3)
Charlson Comorbidity Index										
None	1,469	(62)	333	(50)	168	(55)	92	(46)	2,062	(58)
Moderate	649	(27)	239	(36)	100	(33)	71	(35)	1,059	(30)
Severe	257	(11)	94	(14)	35	(12)	39	(19)	425	(12)
Treatment										
Chemo	662	(28)	118	(18)	73	(24)	43	(21)	896	(25)
R-chemo	1,713	(72)	548	(82)	230	(76)	159	(79)	2,650	(75)
Infection day 43-100										
No	1,995	(84)	425	(64)	209	(69)	85	(42)	2,714	(77)
Yes	380	(16)	241	(36)	94	(31)	117	(58)	832	(23)

Abbreviations: IQR interquartile range; LDH lactate dehydrogenase; ULN upper level of normal; ECOG Eastern cooperative oncology group; NCCN National Comprehensive Cancer Network; IPI International Prognostic Index; R rituximab

Table 2.Types of infection by time period

Category of infection	Early	Late	Early and late	Total
	N %	N %	N %	N %
Febrile neutropenia	247 (37)	75 (25)	74 (37)	396 (34)
CNS infection	1 (<1)	0 (0)	0 (0)	1 (<1)
Septicemia	109 (16)	49 (16)	40 (20)	198 (17)
Pneumonia	86 (13)	52 (17)	23 (11)	161 (14)
Upper respiratory infection	7 (1)	9 (3)	3 (1)	19 (2)
GI infections	28 (4)	11 (4)	9 (4)	48 (4)
Urinary tract infections	34 (5)	17 (6)	8 (4)	59 (5)
Mucositis	17 (3)	9 (3)	3 (1)	29 (2)
Skin infections	30 (5)	27 (9)	6 (3)	63 (5)
Fever, not specified	90 (14)	46 (15)	31 (15)	167 (14)
Other	17 (3)	8 (3)	5 (2)	30 (3)
Total	666 (100)	303 (100)	202 (100)	1,171 (100)

Table 3. Crude and adjusted† HRs for overall survival and event free survival for all patients

		5-year OS		OS unadjusted		OS adjusted		5-year EFS		EFS unadjusted		EFS adjusted	
Infection	N	%	95% CI	HR	95%CI	HR	95%CI	%	95%CI	HR	95% CI	HR	95%CI
None	2,134	74	72-75	1.00	Ref.	1.00	Ref.	67	65-69	1.00	Ref.	1.00	Ref.
Early	560	65	61-69	1.44	1.22-1.69	1.24	1.05-1.47	61	57-75	1.26	1.08-1.47	1.14	0.98–1.34
Late	288	62	56-68	1.61	1.31–1.98	1.32	1.06–1.63	55	49-61	1.55	1.28-1.87	1.30	1.07–1.59
Early and late	191	53	45-60	2.19	1.75–2.74	1.59	1.27–2.00	48	41-55	1.91	1.55–2.36	1.44	1.16–1.79

† Adjusted for NCCN-IPI, comorbidity, sex and rituximab. A total of 459 patients were not included in the adjusted model; missing values in 86 pts and 373 died before day 150

Abbreviations: OS overall survival; EFS event free survival; HR hazard rate ratios; Ref reference; NCCN-IPI National Comprehensive Cancer Network International Prognostic Index

Figure 1. Flow diagram for identification of the study population

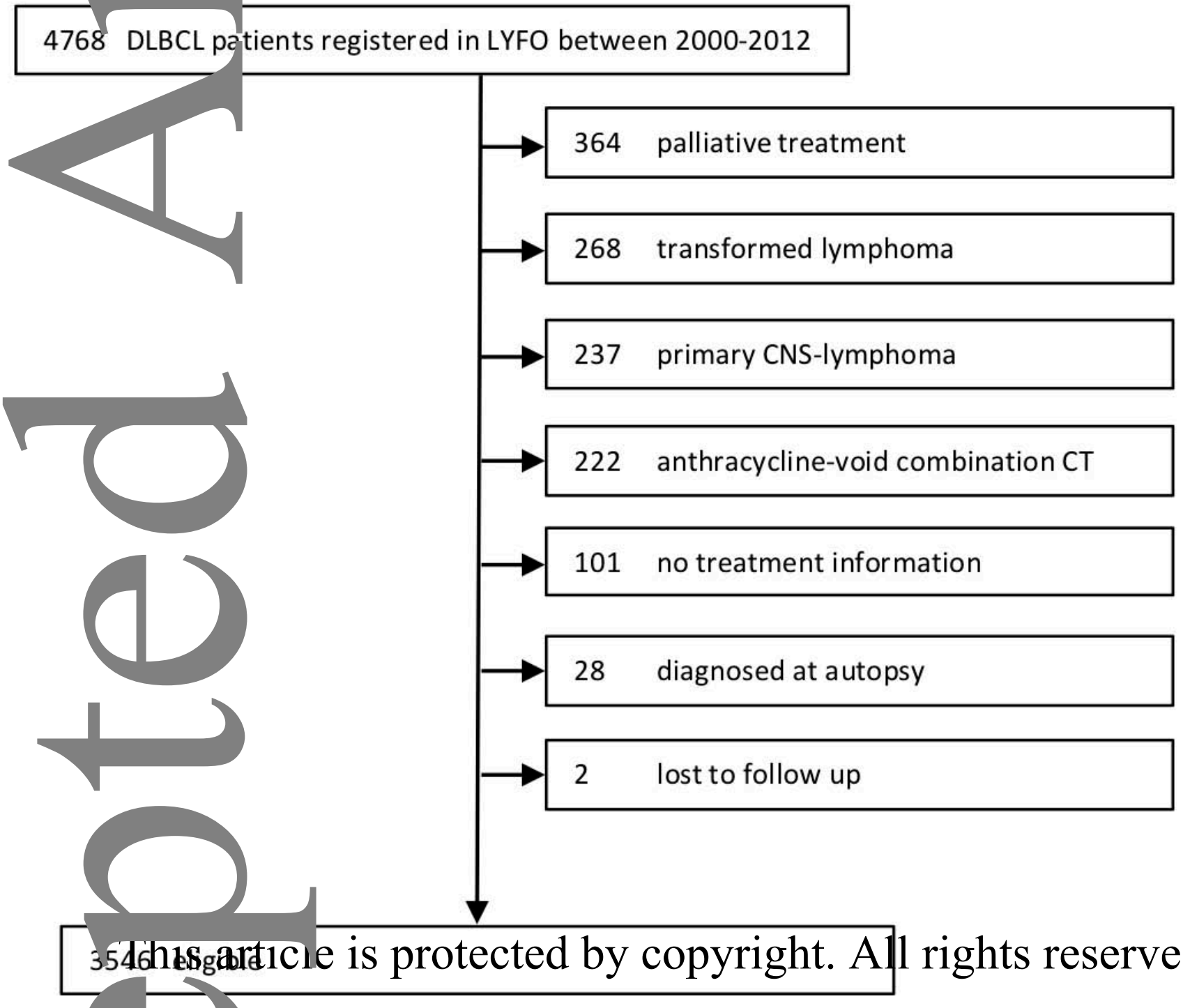
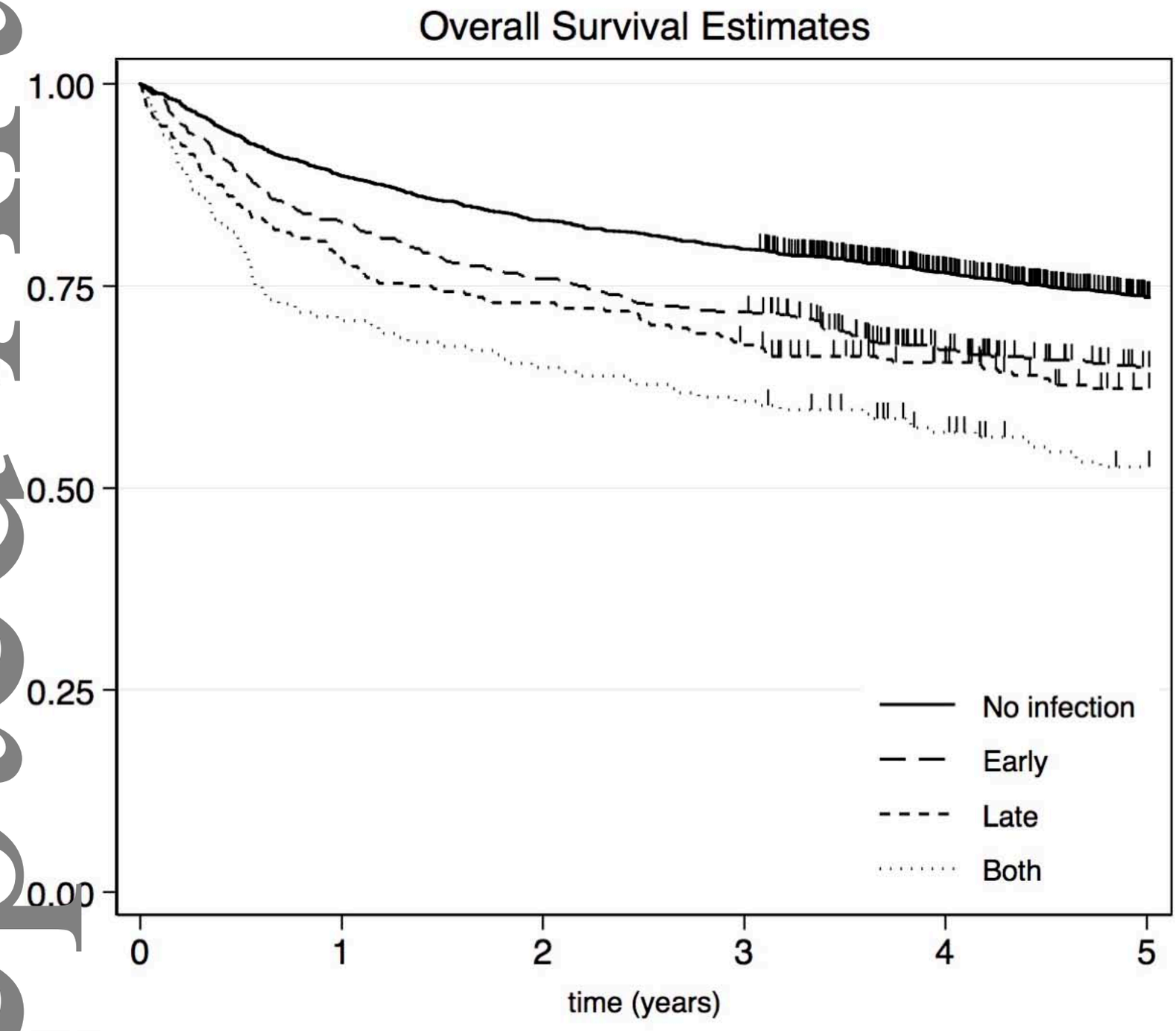


Figure 2. Overall survival for patients according to infectious episodes during treatment



Number at risk

No infection	2134	1891	1773	1698	1500	1298
Early	560	464	425	402	333	288
Late	288	226	210	194	170	146
Both	191	135	124	116	99	85

Figure 3. Overall survival by sex according to period of infection